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Prognostic significance of histopathologically longest tumor size in colorectal cancer

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Abstract

Aim: Colorectal cancer (CRC) accounts for 10% of all cancers diagnosed annually and third cause of cancer-related death in the world. The objective of this study was to investigate the prognostic significance of the histopathologically longest tumor size in colorectal cancer.

Material and Methods: In this retrospective study, we included 337 patients with CRC who were treated in our department. Patients who underwent radical surgery and pathologically confirmed CRC with stages I, II and III were included in the study. Patients' demographic data such as age, gender and body mass index (BMI), tumor localization, pathologic stage, duration of hospitalization, neoadjuvant therapy status, ASA score (The American Society of Anesthesiologists physical status classification system), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), biochemical parameters, total number of lymph nodes, maximum tumor diameter (TuS) and metastatic maximum lymph node diameters and overall survival (OS) were recorded.

Results: The mean age of the patients was 61.78±12.43 years. The mean BMI value was found as 28.29±2.93 kg/m^2 in all patients. Of the patients, 197 (58.5%) were male and 140 (41.5%) were female. Pathological stages were found as I in 48 (14.24%), II in 133 (39.47%) and III in 156 (46.29%) patients. A total of 118 (35.14%) patients received neoadjuvant therapy. The mean operation time was statistically significantly lower in the patients who underwent laparoscopic operations (p=0.011). Maximum tumor size was not significantly correlated with overall survival.

Discussion: Our results indicate that maximum tumor size is not correlated with overall survival, but it was with metastatic maximum lymph node diameter and total number of harvested lymph nodes.

Keywords

Colorectal Cancer, Maximal Tumor Size, Lymph Node, Prognosis, Overall Survival

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Introduction

Colorectal cancer (CRC), represents a significant health problem worldwide. CRC accounts for 10% of all cancers diagnosed annually and third cause of cancer-related death in the world [1]. The incidence and mortality are approximately 25% lower in women than in men [2]. These rates are also different among countries with the highest incidence seen in most developed countries. Based on the continuing progress in developing countries, the worldwide incidence of CRC is estimated to reach 2.5 million new cases by 2035 [3].

Five-year survival in colorectal cancer is 65% [4]. The tumor-lymph node-metastasis (TNM) staging system, which is the gold standard in many cancers, is widely used to evaluate the prognosis and treatment management of patients. The current TNM staging system in American Joint Committee on Cancer (AJCC) Staging Manual 8th edition, is seen as the most important prognostic determinant for CRC. The staging is done by the depth/invasion of the primary tumor in T category, the lymph nodes status in the N category, and the presence of distant metastases in the M category. The size of the primary tumor is not considered in this staging system. However, the prognosis of patients at the same stage is highly variable.

The T classification, based on the vertical tumor penetration level of the different layers of the intestinal wall in microscopic examination, is an important parameter to identify high-risk patients in treatment failure [5]. Tumor size defined as the largest horizontal diameter of the tumor plays an important role in determining the T stage of various solid tumors such as breast, kidney and lung cancers [6].

A significant proportion of CRC patients suffer from recurrence and distant metastasis [7]. Therefore, additional prognostic factors need to be identified to better assess the prognosis. Thus, identification of appropriate prognostic markers is of great importance for decision-making in CRC patients for therapeutic modalities including surgery, molecular target therapy, adjuvant chemotherapy, radiotherapy and novel agents in horizons. Tumor size (TuS) is a surrogate factor of survival in many gastrointestinal cancers including gastric cancer, gastro-intestinal stromal tumor, carcinoid tumors [8]. A recent comprehensive study has clearly shown that tumor size, especially maximum horizontal tumor diameter, represents a valuable prognostic factor in gastric cancer [9]. In pathological examination, tumor size can be considered as a prognostic factor in predicting disease recurrence and survival in patients with colorectal cancer [10]. Some recent studies reveal that large tumor sizes are significantly associated with complications, metastases, high recurrence, and poor prognosis of CRC [11]. However, some other studies suggest that patients with small tumor sizes have a worse prognosis [12, 13]. As a result, its relevance is more unclear with different publications reporting controversial results [13, 14]. The objective of this study was to investigate the prognostic significance of histopathologically longest tumor size in colorectal cancer.

Material and Methods

In this retrospective study, we included 337 patients with CRC who were treated in the gastrointestinal surgery department of our hospital between May 2006 and December 2018. Before the beginning, the study protocol was approved by hospital's local ethics committee with 2020, 4/17-322 numbered protocol. Informed consent from patients was not needed because of the retrospective nature of the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Only patients with workup data and available pathology data including TuS and follow-up data were included. Patients who underwent radical surgery, with pathologically confirmed CRC and patients with stages I, II and III were included in the study. Patients who had synchronous distant metastases at diagnosis (stage IV), patients with more than one primary CRCs, those who underwent emergency surgery and patients with missing data were excluded from the study (Figure 1).

All patients were staged according to AJCC 8th edition. Either laparoscopic or open colorectal surgery was performed by the same surgical team. Tumor size was measured during the histopathological examination. At each follow-up visit, patients underwent physical examinations and were checked for symptoms. Thoracoabdominal computed tomography (CT) scan and tumor markers (CEA, CA19–9) analyses were performed according to the guidelines.

Patients' demographic data such as age, gender and BMI, tumor localization, pathologic stage, duration of hospitalization, neoadjuvant therapy status, ASA score, CEA and CA 19-9 levels, biochemical parameters, harvested total lymph nodes, maximum tumor diameter (TuS) and maximum metastatic lymph node diameter were recorded. In addition, overall survival (OS) was also recorded. Postoperative complications were analyzed using the Clavien Dindo Classification [15] . Correlations of maximum tumor size with other variables were investigated.

Statistical analysis

Data obtained in this study were analyzed using the SPSS

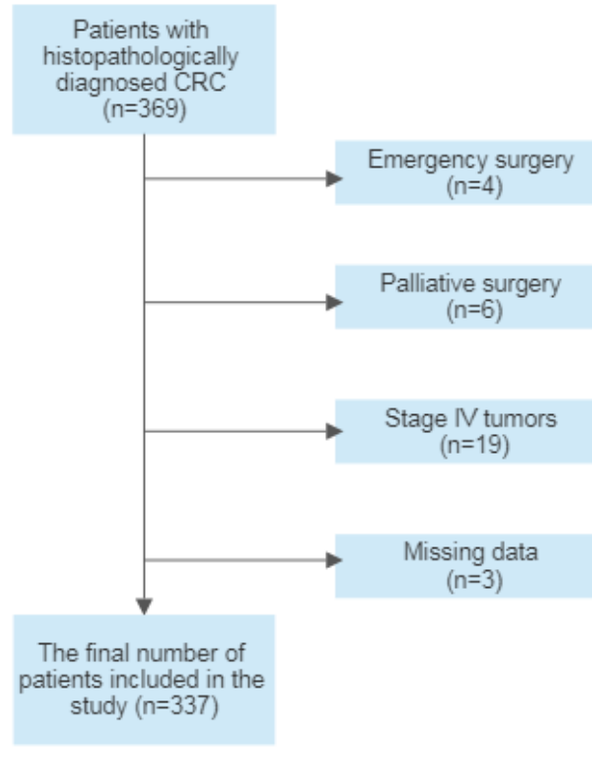

Figure 1. Patient Enrollment

version 25.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. Pearson's correlation analysis was used to determine the correlations between tumor size and other parameters. P<0.05 values were considered statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 337 CRC patients treated and followed-up in our department between May 2006 and December 2018 were included in the study. The mean age was 61.78±12.43 years. The mean BMI value was 28.29±2.93 kg/m^2. Of the patients 197 (58.5%) were male and 140 (41.5%) were female.

The mean age was 62.20±12.34 years for male and 61.49±12.51 years for female patients. The mean BMI values of male and female patients were 27.76±2.74 kg/m^2 and 29.08±3.03 kg/m^2, respectively. No significant difference was found between the genders in terms of age and BMI values (p=0.15 and p=0.30, respectively). ASA scores are shown in Figure 2.

Of all tumors, 35 (10.38%) were found in the cecum, 54 (16.02%) in the ascending colon, 29 (8.61%) in the descending colon, 122 (36.20%) in the rectum, 82 (24.33%) in the sigmoid colon and 15 (4.45%) in the transverse colon. The distribution of the tumor localizations is shown in Figure 3.

The pathological stage was found as I in 48 (14.24%), II in 133 (39.47%), and III in 156 (46.29%). A total of 118 (35.14%) received neoadjuvant therapy. One hundred and twenty (35.61%) underwent open surgery and 217 (64.69%) underwent laparoscopic surgery. The mean operation time was 205.53±26.82 minutes in the open group and 193.83±35.61 minutes in the laparoscopy group. The mean operation time was statistically significantly lower in the patients who underwent laparoscopic operations (p=0.011).

Mean biochemical values and tumor marker levels are shown in Table 1.

Clinical features of the patients are presented in Table 2. The mean duration of hospitalization was 9.61±4.83 days. The mean OS was 51.48±27.74 months. T stage was found as I in 22 (6.53%), II in 62 (18.40%), III in 209 (62.02%) and IV in 44 (13.06%) patients. The mean total number of lymph nodes was 18.75±7.63. The mean maximum tumor size (TuS) was measured as 6.04 ±1.81 cm and the mean metastatic lymph node diameter as 0.92±0.36 cm. Correlations between the maximum tumor size and other several parameters were analyzed using Pearson's correlation analysis (Table 3). As seen in Table 3, the maximum tumor diameter was significantly correlated with maximum metastatic lymph node diameter (r=0.212, p<0.001) and number of harvested lymph nodes (r=0.120, p=0.028). There was no significant correlation between the maximal tumor size and postoperative complications according to the Clavien-Dindo classification (p=0.897). No other significant correlations were found with the maximum tumor diameter.

Discussion

Especially in developed countries, integration of screening

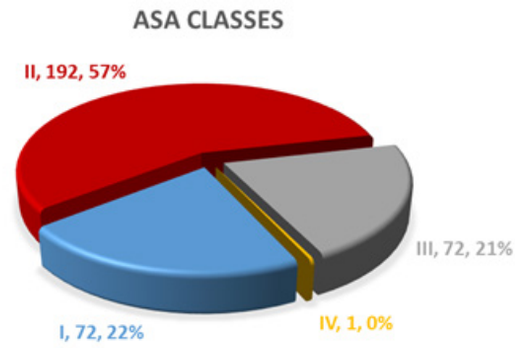

Figure 2. Classes of patients according to ASA

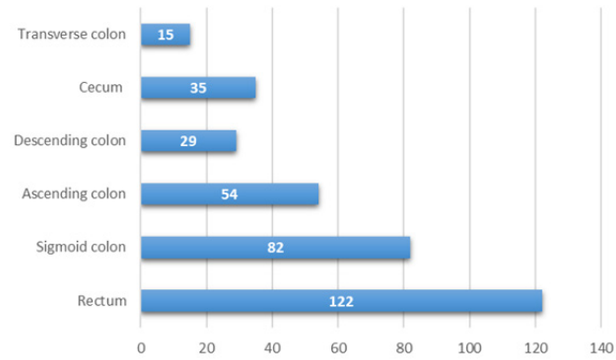

Figure 3. Distribution of tumor localizations

Table 1. Biochemical values and tumor markers of the patients

Parameter	Mean	±Standard Deviation
WBC (10^9/L)	7.11	2.29
Neutrophils (10^9/L)	4.68	1.8
Lymphocytes (10^9/L)	1.62	0.75
Monocytes (10^9/L)	0.55	0.25
Platelets (10^9/L)	284.43	100
CRP (mg/L)	11.58	14
Albumin (g/L)	4.01	0.6
Preop Hct (%)	35.08	4.91
MCV (fL)	78.91	6.96
CEA (µg/L)	8.73	14.47
CA 19-9 (kU/L)	17.51	17.22

Table 2. Clinical features of the patients

Parameter	n	%
T Stage		
I	22	6.53
II	62	18.4
III	209	62.02
IV	44	13.06
	mean	±SD
Hospitalization (days)	9.61	4.83
Overall survival (months)	51.48	27.74
Metastatic Lymph nodes	18.75	7.63
Metastatic lymph node diameter (cm)	0.92	0.36
Maximum tumor size (cm)	6.04	1.81

Table 3. Correlations of maximum tumor size

Correlations		Max tm diameter	OS	Age	Operation Time	Max LN diameter	Total LN	CI-Di
Max tm diameter	Pearson Correlation	1	-0.025	-0.128	-0.017	237**	0.133	0.009
	Sig. (2-tailed)		0.726	0.073	0.813	0.001	0.063	0.897
	N	197	197	197	197	195	196	197
OS	Pearson Correlation	-0.025	1	-0.020	-639**	-243**	-0.072	-0.057
	Sig. (2-tailed)	0.726		0.780	0.000	0.001	0.313	0.430
	N	197	199	197	197	195	196	197
Age	Pearson Correlation	-0.128	-0.020	1	-0.047	-0.021	-0.129	0.058
	Sig. (2-tailed)	0.073	0.780		0.516	0.769	0.072	0.420
	N	197	197	197	197	195	196	197
Operation Time	Pearson Correlation	-0.017	-639**	-0.047	1	0.029	0.109	-0.077
	Sig. (2-tailed)	0.813	0.000	0.516		0.691	0.129	0.280
	N	197	197	197	197	195	196	197
Max LN diameter	Pearson Correlation	237**	-243**	-0.021	0.029	1	194**	0.097
	Sig. (2-tailed)	0.000	0.001	0.769	0.691		0.007	0.176
	N	195	195	195	195	195	194	195
Total LN	Pearson Correlation	0.133	-0.072	-0.129	0.109	194**	1	0.047
	Sig. (2-tailed)	0.028	0.313	0.072	0.129	0.007		0.516
	N	196	196	196	196	194	196	196
Postop Complication	Pearson Correlation	0.009	-0.057	0.058	-0.077	0.097	0.047	1
	Sig. (2-tailed)	0.897	0.430	0.420	0.280	0.176	0.516	
	N	197	197	197	197	195	196	197

**. Correlation is significant at the 0.01 level (2-tailed).

programs into healthcare systems has led to the diagnosis of CRC at earlier stages [16]. It was reported in a study that 38% of colon cancer cases and 43% of rectum cancer cases were diagnosed at an early stage [17]. However, such screening programs are not available in most developing countries and CRC is diagnosed at a locally advanced or metastatic stage with larger tumor size [18]. In such countries, it is of paramount importance to identify prognostic factors to improve outcomes. Pathological stage, lymphovascular invasion, surgical margins, CEA levels, type of tumor, histological grade, bowel obstruction or perforation, genetic mutation, microsatellite instability are among the known prognostic factors in colorectal cancer. Tumor size in CRC refers to the maximum diameter of the tumor specimen examined histopathologically. Its role in T staging has been well established in many cancers including breast, lung and thyroid [19], although its prognostic ability in CRC remains controversial [20-22]. Thus, the prognostic role of maximum tumor size in CRC is investigated in this study.

In the present study, the most common tumor localization was rectum (36.20%) followed by sigmoid colon (24.33%). In a study by Mejri et al., [23] the most common localization was colon (77.04%) followed by rectum (22.96%). In another study by Kornprat et al., the most common tumor localization was colon (56.82%) followed by rectum (43.18%) [20]. These results show that our findings are consistent with the literature.

In our study, we could not find a correlation between maximum tumor size and OS, but tumor size was significantly correlated with the maximum metastatic lymph node diameter and total harvested number of LN. Similarly, in a study by Crozier et al., the maximal tumor diameter was not associated with survival in patients with primary operable CRC [22]. In the same study, maximal tumor size was correlated with pre-operative C-reactive protein (CRP) concentration. In the present study, the asscociation between tumor size and CRP was close to statistical significance (p=0.058). In a large population study (n=300,386) by Saha et al., a tumor size >6 cm increased the risk of overall mortality by 46% compared to those with a tumor size <2 cm after adjusting for sex, age, lymph nodal status and histological grade [11].

There is currently no consensus on a tumor size cut-off in international guidelines [24]. Several studies have suggested that a tumor size of 4 cm has prognostic value. In a study by Mejri et al. investigating the prognostic role of the maximal tumor size in stage II and stage III CRC, 257 patients were included in the study. Patients were divided into two groups according to tumor size as ≤4 cm and >4 cm. The authors reported that tumor size had an impact on survival [23]. Since the majority of our patients had a tumor size >4 cm, we did not make such a grouping. In another study by Kornprat et al., tumor sizes were divided into two groups of ≤4.5 cm and >4.5 cm, and tumor size was demonstrated to be an independent prognostic parameter for CRC patients. In the same study, the cut-off value for tumor size was 3.5 cm. However, optimal cut-off values varied between different parts of the large bowel [20]. It was reported in a study by Dai et al. that tumor size was an independent factor for OS in patients with ulcerative type CRC [25].

Different and controversial results among the studies clearly indicate the need for further studies on tumor size in CRC. Although a cut-off value for tumor size in predicting OS is not determined in this study, cut-off values reported in the literature are also different. Future studies may focus on the prognostic value of tumor size considering tumor stage, lymph node status and diameter, and biochemical parameters.

Study limitations

This study has some limitations. First, it was designed as a retrospective study conducted at a single center. Second, grouping could not be done between tumor sizes, because the majority of tumors were >4 cm. However, given the need for such studies in the literature, it is obvious that further studies on this issue are warranted especially on populations in developing countries.

Conclusion

Our results indicate that maximal tumor size does not correlate with overall survival, but it does correlate with metastatic maximum lymph node diameter and number of harvested lymph nodes. Although it seems to have no effect on OS, it may have an effect on the pathological stage as it affects the lymph node status, and may contribute to TNM classification. Further studies would provide a better insight into prognostic value of tumor size in OS of CRC patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in CA Cancer J Clin. 2020;70(4):313]. CA Cancer J Clin. 2018;68(6):394-424.

2. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet. 2019;394(10207):1467-80.

3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.

4. Brouwer NPM, Bos ACRK, Lemmens VEPP, Tanis PJ, Hugen N, Nagtegaal ID, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer. 2018;143(11):2758-66.

5. Compton CC, Greene FL. The staging of colorectal cancer: 2004 and beyond. CA Cancer J Clin. 2004;54(6):295-308.

6. Giuliano AE, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol. 2018;25(7):1783-85.

7. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data [published correction appears in Lancet Oncol. 2008;9(5):416]. Lancet Oncol. 2007;8(9):784-96.

8. Quan J, Zhang R, Liang H, Li F, Liu H, Zhang H, et al. The impact of tumor size on survival of patients with pT4aN0M0 gastric cancer. Am Surg. 2013;79(3):328-31.

9. Kunisaki C, Makino H, Takagawa R, Oshima T, Nagano Y, Kosaka T, et al. Tumor diameter as a prognostic factor in patients with gastric cancer. Ann Surg Oncol. 2008;15(7):1959-67.

10. Alese OB, Zhou W, Jiang R, Zakka K, Huang Z, Okoli C, et al. Predictive and Prognostic Effects of Primary Tumor Size on Colorectal Cancer Survival. Front Oncol. 2021; 11:728076.

11. Saha S, Shaik M, Johnston G, Saha SK, Berbiglia L, Hicks M, et al. Tumor size predicts long-term survival in colon cancer: an analysis of the National Cancer Data Base. Am J Surg. 2015;209(3):570-4.

12. Santullo F, Biondi A, Cananzi FCM, Fico V, Tirelli F, Ricci R, et al. Tumor size as a prognostic factor in patients with stage IIa colon cancer. Am J Surg. 2018;215(1):71-77.

13. Huang B, Feng Y, Zhu L, Xu T, Huang L, Cai G. Smaller tumor size is associated with poor survival in stage II colon cancer: An analysis of 7,719 patients in the SEER database. Int J Surg. 2016; 33:157-163.

14. Zhai ZW, Gu J. Influence of tumor size on the prognosis in patients with colon cancer. Zhonghua Wei Chang Wai Ke Za Zhi. 2012;15(5):495-8

15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.

16. Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med. 2000;343(22):1603-7.

17. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145-64.

18. Missaoui N, Trabelsi A, Parkin DM, Jaidene L, Chatti D, Mokni M, et al. Trends in the incidence of cancer in the Sousse region, Tunisia, 1993-2006. Int J Cancer. 2010;127(11):2669-77.

19. Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM Classification of Malignant Tumours. 8th ed. Oxford: Wiley Blackwell; 2017. p.51-159.

20. Kornprat P, Pollheimer MJ, Lindtner RA, Schlemmer A, Rehak P, Langner C. Value of tumor size as a prognostic variable in colorectal cancer: a critical reappraisal. Am J Clin Oncol. 2011;34(1):43-49.

21. Feng H, Lyu Z, Zheng J, Zheng C, Wu Q, Liang W, et al. Association of tumor size with prognosis in colon cancer: A Surveillance, Epidemiology, and End Results (SEER) database analysis. Surgery. 2021;169(5):1116-23.

22. Crozier JE, McMillan DC, McArdle CS, Angerson WJ, Anderson JH, Horgan PG, et al. Tumor size is associated with the systemic inflammatory response but not survival in patients with primary operable colorectal cancer. J Gastroenterol Hepatol. 2007;22(12):2288-91.

23. Mejri N, Dridi M, El Benna H, Labidi S, Daoud N, Boussen H. Prognostic value of tumor size in stage II and III colorectal cancer in Tunisian population Colorect. Cancer. 2018;6(4):113–19.

24. Chen K, Collins G, Wang H, Toh JWT. Pathological Features and Prognostication in Colorectal Cancer. Curr Oncol. 2021;28(6):5356-83.

25. Dai W, Li Y, Meng X, Cai S, Li Q, Cai G. Does tumor size have its prognostic role in colorectal cancer? Re-evaluating its value in colorectal adenocarcinoma with different macroscopic growth pattern. Int J Surg. 2017; 45:105-12.

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